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Renovascular disease in older patients beginning renal replacement therapy

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Renovascular disease in older patients beginning renal replacement therapy. Renovascular disease (RVD) in older patients can cause progressive renal insufficiency and even end-stage renal disease (ESRD). The frequency of this clinical problem is not well defined. Renal duplex sonography (RDS) correctly identifies the presence of RVD with an overall accuracy of approximately 95%. Therefore, the purpose of this study was to utilize RDS as a noninvasive tool to identify the presence of critical RVD (≥60% diameter-reducing stenosis or occlusion) in patients 50 years of age or older beginning renal replacement therapy. A total of 53 consecutive participating patients were prospectively interrogated. Complete interrogations occurred in 45 of the 53 patients (85%), and 92 of the 103 kidneys (89%). Critical RVD was noted in 10 of 45 patients (22%). RVD was bilateral in 5 patients, unilateral in 5 patients, and there were 4 renal artery occlusions noted. All patients with critical RVD were white (10 of 25 white patients or 40%). Total pack years of smoking as well as associated cardiovascular and cerebrovascular conditions were greater in those patients with critical RVD compared to those without. These results indicate that RDS remains technically feasible as renal blood flow and function decline. Unsuspected RVD possibly contributory to renal insufficiency exists in a significant number of primarily white patients 50 years of age or older beginning renal replacement therapy. These patients are generally smokers with a high frequency of associated extrarenal atherosclerosis. The addition of RVD as a separate category of disease causing ESRD would improve U.S. Renal Data System ESRD classification. RVD should be recognized as a cause of ESRD.

In recent years, the importance of renovascular disease (RVD) as a cause of progressive renal insufficiency has been emphasized [1, 2]. The frequency of this clinical problem is not well defined, although unsuspected RVD causing renal insufficiency may exist in a significant number of older patients felt clinically to have hypertensive nephropathy [1]. Both autopsy and angiographic studies suggest that RVD is not uncommon with increasing age, especially in patients with evidence of extrarenal atherosclerosis [3]. Additionally, a number of studies suggest that renal artery atherosclerosis may progress and be associated with deterioration in renal function [4, 5]. Furthermore, recent work suggests that approximately 15% of patients 50 years of age or older with end-stage renal disease (ESRD) may have critical RVD as the primary cause [6, 7]. Invasive procedures such as renal artery repair may improve renal function, delay progression of disease and even remove patients from dialysis therapy [8, 9]. Therefore, it is important to identify critical RVD since it may be potentially treatable.

We have found that renal duplex sonography (RDS) correctly identifies the presence of RVD with an overall accuracy of approximately 95% [10]. In our institution, RDS is an ideal screening test for RVD. Exam time is brief, minimal prep is required, and there is no threat to remaining renal function. RDS combines direct visualization of renal architecture with doppler measurement of renal artery blood flow velocity resulting in both anatomic and functional assessment, and it is not affected adversely by bilateral renal artery disease or renal insufficiency. Therefore, the purpose of this study was to utilize RDS as a noninvasive tool to identify the presence of critical RVD, that is ≥ 60% diameter-reducing stenosis or occlusion, in patients 50 years of age or older beginning renal replacement therapy. As will be discussed, the finding of critical RVD does not necessarily imply cause and effect.

Methods

Subjects

Subjects were obtained from patients presenting to the dialysis centers of the Bowman Gray School of Medicine for institution of renal replacement therapy. Ninety consecutive patients 50 years of age or older were prospectively entered into the study over a period of approximately seven months. All patients in the area presenting for renal replacement therapy were captured, as all community and university-affiliated nephrologists allowed their patients to be studied. The protocol was approved by the Clinical Research Practices Committee of the Bowman Gray School of Medicine.

Renal duplex sonography

Subjects were fasted overnight. Renal duplex sonography (RDS) was performed with an Ultramark-9 HDI Ultrasound System (Advanced Technologies Laboratories, Bothell, Washington, USA). This is a fully digitized ultrasound system combining high definition B-scan images with fast-Fourier transform spectral analysis of the Doppler-shifted renal artery signal. A 3.0 mHz mechanical long-focus probe and a 2.25 mHz phased-array probe with color flow imaging were utilized. The technique has been previously described [10]. Briefly, with the patient supine, a B-scan image of the aorta and proximal superior mesenteric artery and left renal vein was obtained. Using the renal vein as a visual

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Table 1. Clinical characteristics of participants versus nonparticipants

Characteristic	Participants ($N = 53$)	Nonparticipants ($N = 37$)	P
Age *years*	65.0 ± 1.1	70.3 ± 1.7	0.007
Black/white	21/32	16/21	NS
Female/male	27/26	15/22	NS
Diagnosis			NS
DM	26	14	
HTN	6	7	
RVD	2	1	
CGN	6	5	
AE	2	2	
CIN	5	4	
UNK	6	4	

Abbreviations are: NS, not significant; DM, diabetic nephropathy; HTN, hypertension nephropathy; RVD, renovascular disease; CGN, chronic glomerulonephritis; AE, atheroembolic disease; CIN, chronic interstitial nephritis; UNK, unknown.

Table 2. Clinical characteristics of participants with complete RDS exam versus incomplete RDS exam

Characteristic	Complete	Incomplete	P
No. of patients	45 (85%)	8 (15%)	
No. of kidneys	92 (89%)	11 (11%)	
Age *years*	65.3 ± 1.2	63.9 ± 1.9	NS
Black/white	20/25	1/7	0.09
Female/male	25/20	2/6	NS
Diagnosis			NS
DM	22	4	
HTN	5	1	
RVD	2	0	
CGN	6	0	
AE	2	0	
CIN	3	2	
UNK	5	1	

Abbreviations as described in Table 1.

reference, the aortic origins of both main renal arteries were identified. Doppler samples were taken from each renal artery from aorta to renal hilum and renal artery peak systolic velocity was calculated. Peak systolic velocities were confirmed using a flank approach and a B-scan image of each kidney was obtained in order to determine kidney length, width and thickness. A study was determined to be negative for critical RVD (< 60% diameter-reducing renal artery stenosis) when renal artery peak systolic velocity from aortic origin to renal hilum was less than 2.0 meters/second. A study was determined to be positive for critical RVD (≥60% diameter-reducing stenosis or occlusion) when a focal renal artery peak systolic velocity ≥ 2.0 meters/second and a distal turbulent Doppler waveform was noted. An artery was noted to be occluded when there was an absence of Doppler shifted signal from an imaged vessel. A RDS exam was noted to be incomplete when renal artery Doppler samples were not obtained from aortic origin to renal hilum.

Data analysis

Demographic data including age, sex, race, and presumed diagnosis causing ESRD were obtained from chart reviews and compared in subjects who were participants versus nonparticipants; in participating subjects with complete versus incomplete RDS exams; and in participating subjects with complete exams who had critical RVD versus no critical RVD. A number of parameters such as hypertension, smoking, associated cardiovascular, cerebrovascular, and peripheral vascular conditions, cholesterol, renal size, and renal functional decline were compared in subjects with critical RVD versus subjects without critical RVD. Where appropriate, results are expressed as means ± SEM. Comparison of group mean values was performed using the Student's t-test. In comparing subgroups, χ^2 analysis was performed utilizing Mantel-Haenszel χ^2 and data were considered statistically significant if $P < 0.05$.

Results

Of the 90 consecutive patients 50 years of age or older who were prospectively entered into the study, 37 refused RDS examination. Many of these patients were old and debilitated and resided in nursing homes, making it difficult for them to come to the Medical Center for RDS examination. Table 1 indicates that there were no differences in race, gender or ESRD diagnoses in the participating versus the nonparticipating subjects. The nonparticipants were older. Therefore, the two groups were comparable and the older age of the nonparticipants would, as will be discussed, only increase the likelihood that critical RVD was present.

Table 2 shows demographic data from those patients with a complete RDS exam versus those patients with an incomplete exam. A total of 53 consecutive participating patients were interrogated. Complete interrogations occurred in 45 of the 53 patients (85%). A total of 103 kidneys were interrogated with a complete study occurring in 92 of the 103 kidneys (89%). These exams are the most difficult that we perform because of the low blood flow and small vessels and kidneys in these patients. However, the results compare rather favorably to our experience in patients without profound renal failure in whom the success rate is closer to 95%. No attempt was made to repeat an incomplete exam after improved bowel prep which would have likely improved the success rate since excess bowel gas impaired a number of these RDS exams. There was no difference in age, gender, race, or ESRD diagnoses in the two groups (Table 2).

Data from the 45 participating patients with complete RDS exams are now presented (Table 3). Critical RVD was noted in 10 of 45 patients (22%). If only white patients were included, 10 of 25 (40%) had critical RVD. RVD was bilateral in five patients, unilateral in five patients, and there were four renal artery occlusions noted. There was a tendency for the patients with RVD to be older, and the minimum age of these patients at the onset of dialysis was older. The most striking finding, however, was that all 10 patients with critical RVD were white. Taken as a whole, the ESRD diagnoses in the two groups were not different.

We compared the history of smoking and hypertension in the two groups (Table 4). Those patients with critical RVD had a tendency toward more years of smoking than those patients without. Total pack years of smoking was greater in those patients with critical RVD. Nine of the 10 patients with critical RVD (90%) were smokers. Both groups, as one would expect, had a very significant history of hypertension. There was no difference in serum cholesterol in the two groups (Table 4).

Table 3. Clinical characteristics of participants with complete RDS exams, RVD versus No RVD

Characteristic	RVD	No RVD	*P*
No. of patients	10 (22%)	35 (78%)	
White patients only	10 (40%)	15 (60%)	
Bilateral/unilateral/occlusion	5/5/4		
Mean age *years*	69.4 ± 2.5	64.1 ± 1.3	0.07
Minimum age *years*	56.3	50.1	
Female/male	5/5	20/15	NS
Black/white	0/10	20/15	0.002
Diagnosis			NS
DM	2	20	
HTN	0	5 (all black)	
RVD	2	0	
CGN	3	3	
AE	1	1	
CIN	1	2	
UNK	1	4	

Abbreviations as described in Table 1.

Table 4. Smoking, hypertension, and cholesterol, RVD versus No RVD

Characteristic	RVD	No RVD	*P*
Smoking *years*	27.7 ± 4.1	16.4 ± 3.0	0.07
Smoking *pack years*	37.4 ± 7.4	17.1 ± 3.8	0.016
Smoking	9 of 10 (90%)	18 of 34 (53%)	0.036
Hypertension *years*	14.7 ± 3.3	12.3 ± 1.9	NS
Hypertension	10 of 10 (100%)	30 of 32 (94%)	NS
Cholesterol *mg/dl*	228.0 ± 28.8	228.7 ± 10.8	NS

NS, not significant.

Table 5. Associated cardiovascular conditions, RVD versus No RVD

Condition	RVD	No RVD	*P*
Angina	5 of 10 (50%)	8 of 34 (24%)	0.111
MI	3 of 10 (30%)	7 of 34 (21%)	NS
CABG	4 of 10 (40%)	4 of 35 (11%)	0.039
Total	7 of 10 (70%)	13 of 35 (37%)	0.068

Abbreviations are: MI, myocardial infarction; CABG, coronary artery bypass grafting; NS, not significant.

Associated cardiovascular conditions in the two groups were compared (Table 5). The percentages of patients with angina, myocardial infarction, and coronary artery bypass grafting were higher in those patients with critical RVD compared with those without. Likewise, associated cerebrovascular conditions such as cerebrovascular accident, transient ischemic attack, and carotid endarterectomy occurred more frequently in the group with critical RVD (Table 6). There was no difference in associated peripheral vascular conditions such as peripheral vascular disease, abdominal aortic aneurysm, or amputation in the two groups (Table 7). Many of the patients without critical RVD had diabetic nephropathy and were prone to other complications of diabetes including amputation.

There was no difference in the rate of renal functional decline over the six months prior to RDS exam, in the groups with and without critical RVD. Kidney size was compared in the two groups (Table 8). No statistically significant differences were noted, although there was a tendency for the difference between right and left kidney size to be greater in the group with critical RVD.

Table 6. Associated cerebrovascular conditions, RVD versus No RVD

Condition	RVD	No RVD	*P*
CVA	3 of 10 (30%)	1 of 35 (3%)	0.009
TIA	2 of 10 (20%)	1 of 35 (3%)	0.058
CEA	1 of 10 (10%)	1 of 35 (3%)	NS
Total	4 of 10 (40%)	2 of 35 (6%)	0.005

Abbreviations are: CVA, cerebrovascular accident; TIA, transient ischemic attack; CEA, carotid endarterectomy; NS, not significant.

Table 7. Associated peripheral vascular conditions, RVD versus No RVD

Condition	RVD	No RVD	*P*
PVD	3 of 10 (30%)	4 of 35 (11%)	NS
AAA	0 of 10 (0%)	2 of 35 (6%)	NS
Amputation	0 of 10 (0%)	3 of 35 (9%)	NS
Total	3 of 10 (30%)	7 of 35 (20%)	NS

Abbreviations are: PVD, peripheral vascular disease; AAA, abdominal aortic aneurysm; NS, not significant.

Table 8. Kidney size, RVD versus No RVD

Kidney size *cm*	RVD	No RVD	*P*
Right	9.5 ± 0.6	10.3 ± 0.2	NS
Left	10.3 ± 0.6	10.3 ± 0.2	NS
Δ	0.9 ± 0.7	0.0 ± 0.2	0.19
Minimum	6.7	7.2	

NS, not significant; Δ difference between left and right.

Discussion

A number of noninvasive screening tests are currently available for diagnosing RVD [11, 12]. We and others have promoted the use of RDS as an ideal screening tool [10–17]. The technique distinguishes between $<60\%$ and $\geq 60\%$ renal artery diameter-reducing stenosis (including occlusion); experimental studies had demonstrated that a 60% diameter-reducing stenosis was required before a decrease in distal renal artery perfusion pressure and blood flow was reproducibly noted [14]. RDS provides both anatomic and functional information regarding renal artery disease, although when used as a percutaneous test RDS does not provide detailed anatomic assessment of renal artery plaque. The sensitivity and specificity of RDS is not adversely affected by bilateral disease, nor by renal insufficiency which increases its utility compared to other screening procedures particularly for the diagnosis of ischemic nephropathy. This explains the rationale for the use of RDS in the present study.

RDS has not been successfully utilized as an accurate screening modality at a number of medical centers. The technique is demanding, and therefore the results are operator-dependent. Success requires a significant commitment in terms of time and effort. At our center, the technique has been validated in two prospective clinical studies comparing RDS with conventional angiography [10, 13]. Combining the results from both studies, 156 patients had renal angiograms available for comparison with RDS. The technique proved to be 94% sensitive, and 98% specific in these 156 patients. In these studies, the overall accuracy of RDS

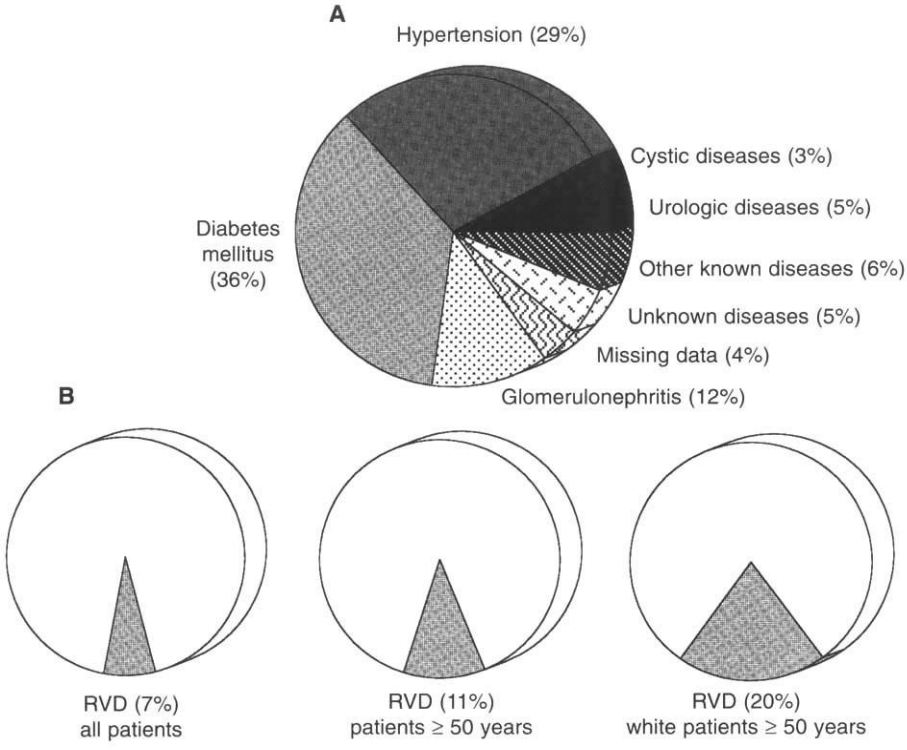

Fig. 1. *United States Renal Data System data from 1994 showing causes of ESRD incidence in the year 1991 [modified from 30]* (**A**). Estimates of yearly incidence of critical RVD causing ESRD in all patients, patients ≥ 50 years, and white patients ≥ 50 years (**B**). These are only estimates, based on data from the present work and [6, 7]. Details are in the text.

was not affected in the subgroup of patients with declining renal function and/or bilateral disease. Therefore, the test is quite reliable at our center.

Excess bowel gas, obesity, and accessory renal arteries can cause technical difficulties with RDS. Excess bowel gas occurred in four of the eight incomplete patient studies. None of these studies were repeated after a bowel prep, under which circumstances a complete study would likely have been possible. This would have improved the success rate to 92%, closer to the 95% experience in patients without profound renal insufficiency. Also, as noted earlier, there were more nonparticipating patients than one would have preferred. However, this was not unexpected, given the poor general health status and nursing home residence of many of these patients. Nonetheless, it should be stressed that the nonparticipants were quite comparable to the participants in terms of race, gender, and diagnosis (Table 1). They were older, and our results indicate that this could only have increased the likelihood of RVD.

This study highlights the common finding of extrarenal atherosclerosis in patients with critical RVD. Based on both autopsy [18] and arteriographic studies [19], it has been known for some time that renal artery disease occurs not infrequently in older individuals. More recently, the rather high prevalence of RVD in patients with extrarenal atherosclerosis involving coronary disease, peripheral vascular disease, and carotid disease has been noted [20–23]. Furthermore, other investigators have shown that RVD may be progressive and may contribute to renal insufficiency and ESRD [4–7, 24–26].

Our prospective work confirms and extends the data of Mailloux et al [6] and Scoble et al [7]. These studies utilized angiography and/or other clinical parameters in order to document RVD as a cause of ESRD in 16.5% [6] and 14% [7] of patients 50 years of age or older entering ESRD programs. We cannot definitively state that all of our patients with critical RVD had ischemic nephropathy as a cause of ESRD. The relationship between RVD and renal insufficiency is not always clear, and therefore the finding of critical RVD does not necessarily imply cause and effect. RDS is a functional tool, and a test positive for critical RVD implies functional impairment of blood flow leading to marked changes in peak systolic velocity as well as distal turbulent Doppler waveforms. While blood flow is impaired, this does not imply causality in terms of ESRD. Some authors believe that the only way to do this is to show improvement after intervention. In this regard, we recently reported our experience in the surgical management of dialysis-dependent ischemic nephropathy [9]. Twenty consecutive patients on dialysis with critical RVD underwent revascularization procedures. At one year post-operative, 14 of 20 (70%) were off dialysis. Overall, retrieval of renal function was observed in 80% of patients with bilateral disease or disease to a solitary kidney, and 33% of patients with unilateral disease. Thus, these findings do suggest that a causal relationship may exist, especially in patients with bilateral disease.

Presumed ESRD diagnoses in our patients with critical RVD covered a spectrum (Table 3). If we include only patients with bilateral disease, then 5 of 45 or 11% may have had ischemic nephropathy. This number, which is very close to that found in the two previously discussed reports [6, 7], is further supported by the following. Three of the five patients actually had renal arteriographic evidence of critical bilateral renal artery stenosis with small kidneys or a discrepancy in kidney size. The fourth patient was a white female smoker with a history of severe hypertension

and small asymmetric kidneys. The fifth patient had evidence of asymmetric kidneys and a renal artery occlusion.

The importance of diagnosing RVD should be underscored for two reasons. These patients do quite poorly on dialysis [6]. Five-year survival is probably only 10% [6]. Secondly, RVD is potentially treatable as we and others have discussed [8, 9, 13, 27–29]. Mortality was statistically significantly reduced in those patients removed from dialysis by operative intervention in our recent report [9].

Figure 1A shows the most recent United States Renal Data System (USRDS) data from 1994 showing ESRD incidence in the year 1991 [30]. This classification indicates the percentage of patients with ESRD due to diabetes mellitus, hypertension, glomerulonephritis, cystic diseases, urologic diseases, other known causes, unknown causes, and missing data. It is interesting to note that RVD is not listed in this classification schema. If we multiply the total number of cases (49,909) by 65% (estimate of patients $\geq$ 50 years), and then multiply again by 11% (estimate of patients with ischemic nephropathy as previously described), we see that 3568 cases of ischemic nephropathy per year may not be correctly classified. Ischemic nephropathy may therefore be the fourth most common cause of ESRD in all patients, accounting for 7% of total cases. Interestingly, in the study by Scoble et al [7], ischemic nephropathy was felt to account for 6% of total cases, remarkably similar results. In patients 50 years of age or older, the estimate as noted previously would be 11% of cases; in white patients 50 years of age or older, the estimate would be 20% of cases based on those 5 of 25 in our study with bilateral disease (Fig. 1B). As noted by Mailloux et al [31], the same classification code is used for arteriolar nephrosclerosis, atheroembolic kidney disease, hypertensive nephropathy, hypertensive renal disease, nephrosclerosis, and renal vascular disease. This clearly results in unnecessary misclassification. We also agree that the category of hypertension (Fig. 1A) is likely overutilized. In our institution, elderly white patients with ESRD are rarely diagnosed with hypertensive ESRD (note zero white cases in Table 3). It is likely that many of these patients are misclassified, and instead have critical RVD or missed primary renal disease [32].

In summary, this study indicates that RDS remains technically feasible as renal blood flow and function decline. In addition, unsuspected RVD possibly contributory to renal insufficiency exists in a significant number of primarily white patients 50 years of age or older beginning renal replacement therapy. These patients are generally smokers with a high frequency of associated extrarenal atherosclerosis. Finally, USRDS should consider adding RVD as a separate category of disease causing ESRD. This would improve ESRD classification and recognition of ischemic nephropathy, a potentially treatable disease.

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